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PATENT APPLICATION TRANSMITTAL LETTER
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Docket No.
BPC077

TO THE ASSISTANT COMMISSIONER FOR PATENTS

JC549 U.S. PTO 09/206833 12/07/98

Transmitted herewith for filing under 35 U.S.C. 111 and 37 C.F.R. 1.53 is the patent application of:

Z. X. Dong et al.

For: **GLP-1 ANALOGUES**

Enclosed are:

- ☒ Certificate of Mailing with Express Mail Mailing Label No. **EE788788292US (3 copies)**
- ☐ sheets of drawings.
- ☐ A certified copy of a application.
- ☒ Declaration ☐ Signed. ☒ Unsigned.
- ☒ Power of Attorney
- ☐ Information Disclosure Statement
- ☐ Preliminary Amendment
- ☒ Other: **Application (Spec: 24 pgs; Claims: 7 pgs; Abstract: 1 pg)**

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	12	- 20 =	0	x $18.00	$0.00
Indep. Claims	1	- 3 =	0	x $78.00	$0.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$760.00
				TOTAL FILING FEE	$760.00

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Dated: December 7, 1998

John D. Conway
Signature

John D. Conway
Attorney for Applicants
Registration No. 39,150

cc:

Patent
Attorney Docket No.: BPC077

NON-PROVISIONAL APPLICATION
UNDER 37 CFR 1.53(b)(1)

TITLE: GLP-1 ANALOGUES

APPLICANTS: ZHENG XIN DONG and DAVID H. COY

EXPRESS MAIL LABEL NO. EE788788292US

PATENT
Attorney Docket No.: BPC077

GLP-1 ANALOGUES

Background of the Invention

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

Glucagon-like peptide-1 (7-36) amide (GLP-1) is synthesized in the intestinal L-cells by tissue-specific post-translational processing of the glucagon precursor pre-proglucagon (Varndell, J.M., et al., J. Histochem Cytochem, 1985:33:1080-6) and is released into the circulation in response to a meal. The plasma concentration of GLP-1 rises from a fasting level of approximately 15 pmol/L to a peak postprandial level of 40 pmol/L. It has been demonstrated that, for a given rise in plasma glucose concentration, the increase in plasma insulin is approximately threefold greater when glucose is administered orally compared with intravenously (Kreymann, B., et al., Lancet 1987:2, 1300-4). This alimentary enhancement of insulin release, known as the incretin effect, is primarily humoral and GLP-1 is now thought to be the most potent physiological incretin in humans. In addition to the insulinotropic effect, GLP-1 suppresses glucagon secretion, delays gastric emptying (Wettergren A., et al., Dig Dis Sci 1993:38:665-73) and may enhance peripheral glucose disposal (D'Alessio, D.A. et al., J. Clin Invest 1994:93:2293-6).

In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM) (Gutniak, M.K., et al., Diabetes Care 1994:17:1039-44). This effect was thought to be mediated both by increased insulin release and by a reduction in glucagon secretion. Furthermore, an intravenous infusion of GLP-1 has been shown to delay postprandial gastric emptying in patients with NIDDM (Williams, B., et al., J. Clin Endo Metab 1996:81:327-32). Unlike sulfonylureas, the insulinotropic action of GLP-1 is dependent on plasma glucose concentration (Holz, G.G. 4th, et al., Nature 1993:361:362-5). Thus, the loss of GLP-1-mediated insulin release at low plasma glucose concentration protects against severe hypoglycemia. This combination of actions gives GLP-1 unique potential therapeutic advantages over other agents currently used to treat NIDDM.

Numerous studies have shown that when given to healthy subjects, GLP-1 potently influences glycemic levels as well as insulin and glucagon concentrations (Orskov, C,

Diabetologia 35:701-711, 1992; Holst, J.J., et al., Potential of GLP-1 in diabetes management in Glucagon III, Handbook of Experimental Pharmacology, Lefevbre PJ, Ed. Berlin, Springer Verlag, 1996, p. 311-326), effects which are glucose dependent (Kreymann, B., et al., Lancet ii: 1300-1304, 1987; Weir, G.C., et al., Diabetes 38:338-342, 1989). Moreover, it is also effective in patients with diabetes (Gutniak, M., N. Engl J Med 226:1316-1322, 1992; Nathan, D.M., et al., Diabetes Care 15:270-276, 1992), normalizing blood glucose levels in type 2 diabetic subjects (Nauck, M.A., et al., Diagbetologia 36:741-744, 1993), and improving glycemic control in type 1 patients (Creutzfeldt, W.O., et al., Diabetes Care 19:580-586, 1996), raising the possibility of its use as a therapeutic agent.

GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. Exogonously administered GLP-1 is also rapidly degraded (Deacon, C.F., et al., Diabetes 44:1126-1131, 1995). This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.

Summary of the Invention

In one aspect, the present invention is directed to a compound of formula (I),

$$(R^2R^3)\text{-} A^7\text{-}A^8\text{-}A^9\text{-}A^{10}\text{-}A^{11}\text{-}A^{12}\text{-}A^{13}\text{-}A^{14}\text{-}A^{15}\text{-}A^{16}\text{-}A^{17}\text{-}A^{18}\text{-}A^{19}\text{-}A^{20}\text{-}A^{21}\text{-}A^{22}\text{-}A^{23}\text{-}A^{24}\text{-}A^{25}\text{-}A^{26}\text{-}A^{27}\text{-}A^{28}\text{-}A^{29}\text{-}A^{30}\text{-}A^{31}\text{-}A^{32}\text{-}A^{33}\text{-}A^{34}\text{-}A^{35}\text{-}A^{36}\text{-}A^{37}\text{-} R^1,$$

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, D-His, Tyr, 3-Pal, 4-Pal, Hppa, Tma-His, Amp or deleted, provided that when A^7 is Ura, Paa, Pta or Hppa then R^2 and R^3 are deleted;

A^8 is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala, Arg or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, Ala, D-Ala, Phe or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β-Nal, Cha, Trp or X^1-Phe;

A^{13} is Thr or Ser;

A^{14} is Ser, Thr, Ala or Aib;

A^{15} is Asp, Ala, D-Asp or Glu;

A^{16} is Val, D-Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala, D-Ala, Tba or Cha;

A^{17} is Ser, Ala, D-Ala, Aib, Acc or Thr;

A^{18} is Ser, Ala, D-Ala, Aib, Acc or Thr;

A^{19} is Tyr, D-Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β-Nal, Amp or X^1-Phe;

A^{20} is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X^1-Phe;

A^{21} is Glu, Ala or Asp;

A^{22} is Gly, Acc, Ala, D-Ala, β-Ala or Aib;

A^{23} is Gln, Asp, Ala, D-Ala, Aib, Acc, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{26} is Lys, Ala, 3-Pal, 4-Pal, Arg, hArg, Orn, Amp, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{27} is Glu, Ala, D-Ala or Asp;

A^{28} is Phe, Ala, Pal, β-Nal, X^1-Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala, Tba or Phe;

A^{30} is Ala, Aib, Acc or deleted;

A^{31} is Trp, Ala, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib, Cha, Amp or deleted;

A^{32} is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X^1-Phe, Ala or deleted;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, X^1-Phe, Tba, Gaba or deleted;

A^{34} is Lys, Arg, hArg, Orn, Amp, Gaba, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) or deleted;

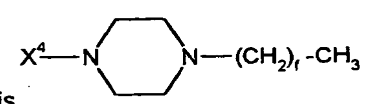
A^{35} is Gly or deleted;

A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, Amp, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) or deleted;

A^{37} is Gly or deleted;

X^1 for each occurrence is independently selected from the group consisting of (C_1-C_6)alkyl, OH and halo;

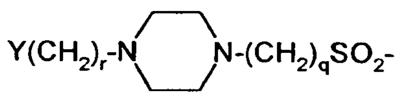
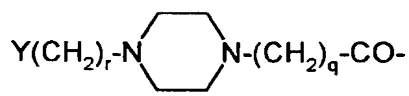
R^1 is OH, NH_2, (C_1-C_{12})alkoxy, or NH-X^2-CH_2-Z, wherein X^2 is a (C_1-C_{12})hydrocarbon moiety, and Z is H, OH, CO_2H or $CONH_2$;

X^3 is 

or –C(O)-NHR^{12}, wherein X^4 for each occurrence is independently -C(O)-, -NH-C(O)- or -CH_2-, and f for each occurrence is independently an integer from 1 to 29;

each of R^2 and R^3 is independently selected from the group consisting of H, (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, and

hydroxynaphthyl(C_1-C_{30})alkyl; or one of R^2 and R^3 is $C(O)X^5$ in which X^5 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, hydroxynaphthyl(C_1-C_{30})alkyl, $(CH_3)_2\text{-}N\text{-}\overset{\uparrow}{C}{=}\overset{+}{N}(CH_3)_2$,

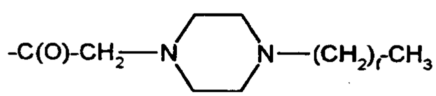
 or  ,

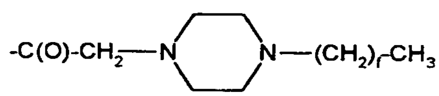
(a) (b)

where Y is H or OH, r is 0-4 and q is 0-4;

n for each occurrence is independently an integer from 1-5; and

R^{10} and R^{11} for each occurrence is each independently H, (C_1-C_{30})alkyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, –C((NH)(NH_2)) or



, provided that when R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, –C((NH)(NH_2)) or  , R^{11} is H or (C_1-C_{30})alkyl; and

R^{12} is (C_1-C_{30})alkyl;

with the proviso that:

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, or -37)NH_2 or hGLP-1(7-36, or -37)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, or -37)NH_2 or hGLP-1(7-36, or -37)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not [Lys^{26}(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, [Lys^{34}(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, [$Lys^{26,34}$-bis(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, [Arg^{26}, Lys^{34}(N^{ε}-alkanoyl)]hGLP-1(8-36, or -37)-E, or [$Arg^{26,34}$, Lys^{36}(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, wherein E is -OH or -NH_2;

(iv) a compound of formula (I) is not Z-hGLP-1(7-36, or -37)-OH, Z-hGLP-1(7-36, or -37)-NH_2, where Z is selected from the group consisting of

(a) [Arg^{26}], [Arg^{34}], [$Arg^{26,34}$], [Lys^{36}], [Arg^{26}, Lys^{36}], [Arg^{34}, Lys^{36}], [D-Lys^{36}], [Arg^{36}], [D-Arg^{36}], [$Arg^{26,34}$, Lys^{36}] or [$Arg^{26,36}$, Lys^{34}];

(b) [Asp^{21}];

(c) at least one of [Aib^{8}], [D-Ala^{8}] and [Asp^{9}]; and

(d) [Tyr^{7}], [N-acyl-His^{7}], [N-alkyl-His^{7}], [N-acyl-D-His^{7}] or [N-alkyl-D-His^{7}];

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not [N-Me-Ala^{8}]hGLP-1(8-36 or -37), [Glu^{15}]hGLP-1(7-36 or -37), [Asp^{21}]hGLP-1(7-36 or -37) or [Phe^{31}]hGLP-1(7-36 or -37).

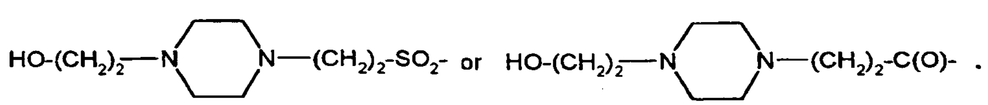
A preferred compound of the immediately foregoing compound of formula (I) is where A^{11} is Thr; A^{13} is Thr; A^{14} is Ser, Aib or Ala; A^{17} is Ser, Ala, Aib or D-Ala; A^{18} is Ser, Ala, Aib or D-Ala; A^{21} is Glu or Ala; A^{23} is Gln, Glu, or Ala; and A^{27} is Glu or Ala; or a pharmaceutically acceptable salt thereof.

A preferred compound of the immediately foregoing compound of formula (I) is where A^{9} is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc or Aic; A^{16} is Val, D-Val, Acc, Aib, Ala, Tle or D-Ala; A^{19} is Tyr, 3-Pal, 4-Pal or D-Tyr; A^{20} is Leu, Acc, Cha, Ala or Tle; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-NH-R^{10})-C(O); A^{28} is Phe or Ala; A^{29} is Ile, Acc or Tle; A^{30} is Ala, Aib or deleted; A^{31} is Trp, Ala, 3-Pal, 4-Pal or deleted; A^{32} is Leu, Acc, Cha, Ala or deleted; A^{33} is Val, Acc, Ala, Gaba, Tle or deleted; or a pharmaceutically acceptable salt thereof.

A preferred compound of the immediately foregoing compound of formula (I) is where A^{8} is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly, Ala, D-Ala or Phe; A^{12} is Phe, A6c or A5c; A^{16} is Val, Ala, Tle, A6c, A5c or D-Val; A^{20} is Leu, A6c, A5c, Cha, Ala or Tle; A^{22} is Gly, Aib, β-Ala, L-Ala or D-Ala; A^{24} is Ala or Aib; A^{29} is Ile, A6c, A5c or Tle; A^{32} is Leu, A6c, A5c, Cha, Ala or deleted; A^{33} is Val, A6c, A5c, Ala, Gaba, Tle or deleted; or a pharmaceutically acceptable salt thereof.

A preferred compound of the immediately foregoing compound of formula (I) is where R^{1} is OH or NH_2 or a pharmaceutically acceptable salt thereof.

A preferred compound of the immediately foregoing compound of formula (I) or a pharmaceutically acceptable salt thereof is where R^{2} is H and R^{3} is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, (C_1-C_{30})acyl,



A most preferred compound of formula (I) is where said compound is

[D-Ala^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]-GLP-1(7-34)NH$_2$; [D-Ala^{8,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH$_2$; [Ala^{18,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH$_2$; [Ala^{16,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH$_2$; [Ala^{14,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH$_2$; [Ala^{22,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH$_2$; [Hppa^{7}]hGLP-1(7-36)-NH$_2$; [Ala^{15,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH$_2$; [Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH$_2$; [Ala^{22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{15,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{21,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{22,23,27,32}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [Ala^{22,23,27,31}, 3-Pal^{19}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [Ala^{22,23,27,28}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [Ala^{22,23,27,29}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [Ala^{23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [Ala^{20,22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [Ala^{22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [D-Ala^{10}, Ala^{22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH$_2$; [D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH$_2$; [Ala^{17,23,27}, 3-Pal^{19,26,31}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8}, Ala^{17}, 3-Pal^{19,31}]hGLP-1(7-34)-NH$_2$; [Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Tle^{29}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Tle^{16}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [D-Ala^{22}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Aib^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH$_2$; [Aib^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH$_2$; [Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Ala^{17,23,27}, 3-Pal^{19,31}, Tle^{33}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [Tle^{16}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [N-Me-D-Ala^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH$_2$; [Aib^{8}, Ala^{17,18,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH$_2$; [Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle^{16,20}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8}, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle^{16}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8,22}, Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8,18}, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; [D-Ala^{8,17}, Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; or [D-Ala^{8}, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH$_2$; or a pharmaceutically acceptable salt thereof.

Another most preferred compound of formula (I) is wherein said compound is [Aib^{8}, A6c^{32}]hGLP-1(7-36)NH$_2$; [A6c^{20,32}]hGLP-1(7-36)-NH$_2$; [Aib^{8}]hGLP-1(7-36)-NH$_2$; [(Tma-His)^{7}]hGLP-1(7-36)-NH$_2$; [A6c^{8}]hGLP-1(8-36)-NH$_2$; [A6c^{8}]hGLP-1(7-36)-NH$_2$; [A6c^{16,20}]hGLP-1(7-36)-NH$_2$; [A6c^{29,32}]hGLP-1(7-36)-NH$_2$; [A6c^{20}, Aib^{24}]hGLP-1(7-36)-NH$_2$; [Aib^{24}, A6c^{29,32}]hGLP-1(7-36)-NH$_2$; [A6c^{16,29,32}]hGLP-1(7-36)-NH$_2$; [Ura^{7}]hGLP-1(7-36)-NH$_2$; [Paa^{7}]hGLP-1(7-36)-NH$_2$; [Pta^{7}]hGLP-1(7-36)-NH$_2$; [N-Me-Ala^{8}]hGLP-1(7-36)-NH$_2$; [N-Me-

D-Ala^8]hGLP-1(7-36)-NH_2; [N-Me-D-Ala^8]hGLP-1(8-36)-NH_2; [N-Me-Gly^8]hGLP-1(7-36)-NH_2; [A5c^8]hGLP-1(7-36); [N-Me-Glu^9]hGLP-1(7-36)-NH_2; [A5c^8, A6c^{20,32}]hGLP-1(7-36)-NH_2; [Aib^8, A6c^{32}]hGLP-1(7-36)-NH_2; [Aib^{8,25}]hGLP-1(7-36)-NH_2; [Aib^{8,24}]hGLP-1(7-36)-NH_2; [Aib^{8,30}]hGLP-1(7-36)-NH_2; [Aib^8, Cha^{20}]hGLP-1(7-36)-NH_2; [Aib^8, Cha^{32}]hGLP-1(7-36)-NH_2; [Aib^8, Glu^{23}]hGLP-1(7-36)-NH_2; [Aib^8, A6c^{20}]hGLP-1(7-36)-NH_2; [Aib^8, A6c^{20,32}]hGLP-1(7-36)-NH_2; [Aib^{8,22}]hGLP-1(7-36)-NH_2; [Aib^8,β-Ala^{22}]hGLP-1(7-36)-NH_2; [Aib^8, Lys^{25}]hGLP-1(7-36)-NH_2; [Aib^8, A6c^{12}]hGLP-1(7-36)-NH_2; [Aib^8, A6c^{29}]hGLP-1(7-36)-NH_2; [Aib^8, A6c^{33}]hGLP-1(7-36)-NH_2; [Aib^{8,14}]hGLP-1(7-36)NH_2; [Aib^{8,18}]hGLP-1(7-36)NH_2; or [Aib^{8,17}]hGLP-1(7-36)NH_2; or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

In still another aspect, the present invention provides a method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof.

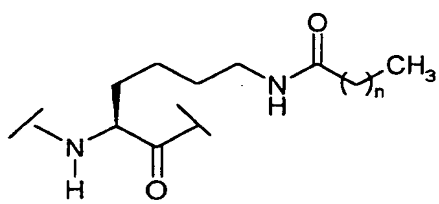
In yet a further aspect, this invention provides a method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof. Preferred of the foregoing method is where the disease is Type I diabetes or Type II diabetes.

With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side chain of an amino acid (e.g., CH_3 for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R^2R^3)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R^2 and R^3 are as defined above except in the case where A^7 is Ura, Paa, Pta or Hppa in which case R^2 and R^3 are not present since Ura, Paa, Pta and Hppa are considered here as des-amino amino acids. The abbreviations: β-Nal, Nle, Cha, Amp, 3-Pal, 4-Pal and Aib stand for the following α-amino acids: β-(2-naphthyl)alanine, norleucine, cyclohexylalanine, 4-amino-phenylalanine, β-(3-pyridinyl)alanine, β-(4-pyridinyl)alanine and α-aminoisobutyric

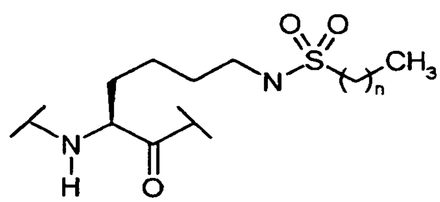
acid, respectively. Other amino acid definitions are: Ura is urocanic acid; Pta is (4-pyridylthio) acetic acid; Paa is *trans*-3-(3-pyridyl) acrylic acid; Tma-His is N,N-tetramethylamidino-histidine; N-Me-Ala is N-methyl-alanine; N-Me-Gly is N-methyl-glycine; N-Me-Glu is N-methyl-glutamic acid; Tle is *tert*-butylglycine; Abu is α-aminobutyric acid; Tba is *tert*-butylalanine; Orn is ornithine; Aib is α-aminoisobutyric acid; β-Ala is β-alanine; Gaba is γ-aminobutyric acid; Ava is 5-aminovaleric acid; and Aic is 2-aminoindane-2-carboxylic acid.

What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid (A3c); 1-amino-1-cyclobutanecarboxylic acid (A4c); 1-amino-1-cyclopentanecarboxylic acid (A5c); 1-amino-1-cyclohexanecarboxylic acid (A6c); 1-amino-1-cycloheptanecarboxylic acid (A7c); 1-amino-1-cyclooctanecarboxylic acid (A8c); and 1-amino-1-cyclononanecarboxylic acid (A9c). In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COX^5 stands for $-C{=}O{\cdot}X^5$. Examples of $-C{=}O{\cdot}X^5$ include, but are not limited to, acetyl and phenylpropionyl.

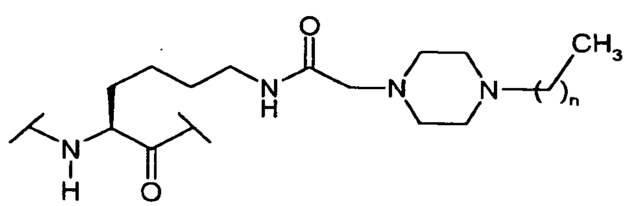
What is meant by Lys(N^ε-alkanoyl) is represented by the following structure:



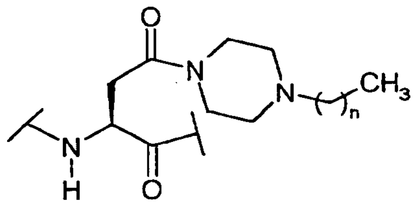
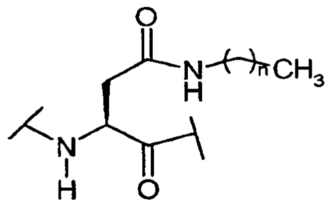
. What is meant by Lys(N^ε-alkylsulfonyl) is represented by the following structure:



. What is meant by Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) is represented by the following structure:



. What is meant by Asp(1-(4-alkyl-piperazine)) is represented by the following

structure:  . What is meant by Asp(1-alkylamino) is represented by the following structure:  . The variable n in the foregoing structures is 1 to 30.

The full names for other abbreviations used herein are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2ClZ for 2-chlorobenzyloxycarbonyl and OcHex for O-cyclohexyl.

A peptide of this invention is also denoted herein by another format, e.g., $[A5c^8]hGLP\text{-}1(7\text{-}36)NH_2$, with the substituted amino acids from the natural sequence placed between the set of brackets (e.g., $A5c^8$ for Ala^8 in hGLP-1). The abbreviation GLP-1 means glucagon-like peptide-1. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hGLP-1(7-36) is amino acids 7 through 36 of the peptide sequence for human GLP-1). The sequence for hGLP-1(7-37) is listed in Mojsov, S., Int. J. Peptide Protein Res,. 40, 1992, pp. 333-342. The designation "NH_2" in $hGLP\text{-}1(7\text{-}36)NH_2$ indicates that the C-terminus of the peptide is amidated. hGLP-1(7-36) means that the C-terminus is the free acid.

Detailed Description

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R^2 and R^3 of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., $(C_1\text{-}C_{30})$alkyl, can be attached using reductive alkylation. Hydroxyalkyl groups, e.g., $(C_1\text{-}C_{30})$hydroxyalkyl, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g.,

COE^1, may be attached by coupling the free acid, e.g., E^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

When R^1 is NH-X^2-CH_2-Z (Z=$CONH_2$), the synthesis of the peptide starts with BocHN-X^2-CH_2-COOH which is coupled to the MBHA resin. If R^1 is NH-X^2-CH_2-COOH (Z=COOH) the synthesis of the peptide starts with Boc-HN-X^2-CH_2-COOH which is coupled to PAM resin.

The following describes a synthetic method for making a peptide of this invention, which method is well-known to those skilled in the art. Other methods are also known to those skilled in the art.

Benzhydrylamine-polystyrene resin (Advanced ChemTech, Inc., Louisville, KY) (0.9 g, 0.3 mmole) in the chloride ion form is placed in a reaction vessel of an Advanced ChemTech Peptide Synthesizer Model 200 programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 15 min each); (c) methylene chloride; (d) ethanol; (e) methylene chloride; (f) 10% diisopropylethylamine in methylene chloride.

The neutralized resin is stirred with Boc-protected amino acid which is to be the C-terminal amino acid of the desired peptide to be synthesized and diisopropylcarbodiimide (3 mmole each) in methylene chloride for 1 hour and the resulting amino acid resin is then cycled through steps (a) through (f) in the above wash program. The other amino acids (3 mmol) of the desired peptide are then coupled successively by the same procedure. The finished peptide is cleaved from the resin by mixing it with anisole (5 ml), dithiothreitol (100 mg) and anhydrous hydrogen fluoride (35 ml) at about 0 °C and stirring it for about 45 min. Excess hydrogen fluoride is evaporated rapidly under a stream of dry nitrogen and free peptide precipitated and washed with ether. The crude peptide is then dissolved in a minimum volume of dilute acetic acid and eluted on a column (2.5 x 25 cm) of VYDAC® octadecylsilane silica (10 mM) and eluted with a linear gradient of 20-60% acetonitrile over about 1 h in 0.1% trifluoroacetic acid in water. Fractions are examined by thin layer chromatography and analytical high performance liquid chromatography (40-70% B at 1%/min, solution B is 80% acetonitrile/water containing 0.1% TFA) and pooled to give maximum purity rather than yield. Repeated lyophilization of the solution from water gives the product as a white, fluffy powder.

The product peptide is analyzed by HPLC. Amino acid analysis of an acid hydrolysate of the product peptide can confirm the composition of the peptide. Laser desorption MS is used to determine the molecular weight of the peptide.

The protected amino acid 1-[N-tert-butoxycarbonyl-amino]-1-cyclohexane-carboxylic acid (Boc-A6c-OH) was synthesized as follows. 19.1 g (0.133 mol) of 1-amino-1-cyclohexanecarboxylic acid (Acros Organics, Fisher Scientific, Pittsburgh, PA) was dissolved in 200 ml of dioxane and 100 ml of water. To it was added 67 ml of 2N NaOH. The solution was cooled in an ice-water bath. 32.0 g (0.147 mol) of di-tert-butyl-dicarbonate was added to this solution. The reaction mixture was stirred overnight at room temperature. Dioxane was then removed under reduced pressure. 200 ml of ethyl acetate was added to the remaining aqueous solution. The mixture was cooled in an ice-water bath. The pH of the aqueous layer was adjusted to about 3 by adding 4N HCl. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (1 x 100 ml). The two organic layers were combined and washed with water (2 x 150 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The residue was recrystallized in ethyl acetate/hexanes. 9.2 g of the pure product was obtained. 29% yield.

Boc-A5c-OH was synthesized in an analogous manner to that of Boc-A6c-OH. Other protected Acc amino acids can be prepared in an analogous manner by a person of ordinary skill in the art as enabled by the teachings herein.

In the synthesis of a peptide of this invention containing A5c, A6c and/or Aib, the coupling time is about 2 hrs. for these residues and the residue immediately following them. For the synthesis of [Tma-His^7]hGLP-1(7-36)NH_2, HBTU (2 mmol) and DIEA (1.0 ml) in 4 ml DMF were used to react with the N-terminal free amine of the peptide-resin in the last coupling reaction; the coupling time is about 2 hours.

The full names for the abbreviations used above are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2ClZ for 2-chlorobenzyloxycarbonyl, 2BrZ for 2-bromobenzyloxycarbonyl and OcHex for O-cyclohexyl.

The substituents R^2 and R^3 of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example,

alkyl groups, e.g., (C_1-C_{30})alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COX^1, can be attached by coupling the free acid, e.g., X^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for about one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

A compound of the present invention can be tested for activity as a GLP-1 binding compound according to the following procedure.

Cell Culture:

RIN 5F rat insulinoma cells (ATCC-# CRL-2058, American Type Culture Collection, Manassas, VA), expressing the GLP-1 receptor, were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, and maintained at about 37 °C in a humidified atmosphere of 5% CO_2/95% air.

Radioligand Binding:

Membranes were prepared for radioligand binding studies by homogenization of the RIN cells in 20 ml of ice-cold 50 mM Tris-HCl with a Brinkman Polytron (Westbury, NY) (setting 6, 15 sec). The homogenates were washed twice by centrifugation (39,000 g / 10 min), and the final pellets were re-suspended in 50 mM Tris-HCl, containing 2.5 mM $MgCl_2$, 0.1 mg/ml bacitracin (Sigma Chemical, St. Louis, MO), and 0.1% BSA. For assay, aliquots (0.4 ml) were incubated with 0.05 nM [^{125}I]GLP-1(7-36) (~2200 Ci/mmol, New England Nuclear, Boston, MA), with and without 0.05 ml of unlabeled competing test peptides. After a 100 min incubation (25 °C), the bound [^{125}I]GLP-1(7-36) was separated from the free by rapid filtration through GF/C filters (Brandel, Gaithersburg, MD), which had been previously soaked in 0.5% polyethyleneimine. The filters were then washed three times with 5 ml aliquots of ice-cold 50 mM Tris-HCl, and the bound radioactivity trapped on the filters was counted by gamma spectrometry (Wallac LKB, Gaithersburg, MD). Specific binding was defined as the total [^{125}I]GLP-1(7-36) bound minus that bound in the presence of 1000 nM GLP1(7-36) (Bachem, Torrence, CA).

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid,

sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB, C-8). The column is eluted with (1) 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of GLP-1 is varied and multitudinous [See, Todd, J.F., et al., Clinical Science, 1998, 95, pp. 325-329; and Todd, J.F. et al., European Journal of Clinical Investigation, 1997, 27, pp.533-536]. Thus, the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself. These varied uses of GLP-1 may be summarized as follows, treatment of: Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system diseases, restenosis and neurodegenerative diseases. GLP-1 analogues of the present invention that elicit an antagonist effect from a subject can be used for treating the following: hypoglycemia and malabsorption syndrome associated with gastroectomy or small bowel resection.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) in association with a pharmaceutically acceptable carrier or diluent.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of 1×10^{-7} to 200 mg/kg/day, preferably 1×10^{-4} to 100 mg/kg/day, which can be administered as a single dose or divided into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S.

Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of a bioactive agent. U.S. Application No. 09/121,653 filed July 23, 1998, teaches a process for making microparticles comprising a therapeutic agent such as a peptide in an oil-in-water process. U.S. Application No. 09/131,472 filed August 10, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. U.S. Application No. 09/184,413 filed November 2, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and applications are incorporated herein by reference.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and is not meant to limit the scope of the present invention in any manner.

Example 1

[D-Ala^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]-GLP-1(7-34)NH_2

Benzhydrylamine-polystyrene resin (Advanced ChemTech, Inc. Louisville, KY) (0.9 g, 0.3 mmole) in the chloride ion form was placed in a reaction vessel of an Advanced ChemTech peptide synthesizer Model 200 programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 15 min each); (c) methylene chloride; (d) ethanol; (e) methylene chloride; (f) 10% diisopropylethylamine in methylene chloride.

The neutralized resin was stirred with Boc-Gaba and diisopropylcarbodiimide (3 mmole each) in methylene chloride for 1 hour and the resulting amino acid resin was then cycled through steps (a) to (f) in the above wash program. The following amino acids (3

mmole) were then coupled successively by the same procedure: Boc-Val, Boc-Leu, Boc-3-Pal, Boc-Ala, Boc-Ile, Boc-Phe, Boc-Ala, Boc-Lys(2-Cl-Z), Boc-Ala, Boc-Ala, Boc-Ala, Boc-Ala, Boc-Glu(Bzl), Boc-Leu, Boc-3-Pal, Boc-Ser(Bzl), Boc-Ala, Boc-Val, Boc-Asp(Bzl), Boc-Ser(Bzl), Boc-Thr(Bzl), Boc-Phe, Boc-Thr(Bzl), Boc-Gly, Boc-Glu(Bzl), Boc-D-Ala, Boc-His(Bom).

The resin with the completed peptide sequence was mixed with anisole (5 ml), dithiothreitol (100 mg) and anhydrous hydrogen fluoride (35 ml) at about 0 °C and stirred for about 45 min. Excess hydrogen fluoride was evaporated rapidly under a stream of dry nitrogen and free peptide precipitated and washed with ether. The crude peptide was then dissolved in a minimum volume of dilute acetic acid and eluted on a column (2.5 x 25 cm) of VYDAC® octadecylsilane silica (10 mM) and eluted with a linear gradient of 20-60% acetonitrile over about 1 h in 0.1% trifluoroacetic acid in water. Fractions were examined by thin layer chromatography and analytical high performance liquid chromatography (40-70% B at 1%/min; r.t.: 14.1 min) and pooled to give maximum purity rather than yield. Repeated lyophilization of the solution from water gives the product (49.9 mg) as a white, fluffy powder.

The product was found to be homogeneous by HPLC and tlc. Amino acid analysis of an acid hydrolysate confirms the composition of the peptide. Laser desorption MS gave a MW of 2880 (Calc. M+H 2873).

Example 2

Synthesis of Peptide Lower-Alkylamides

Peptides are assembled on O-benzyl-polystyrene resin (often referred to as Merrifield resin) using the Boc amino acid protocol described in Example 1, except that Asp and Glu amino acid carboxyl side-chains are protected with an Fm (fluorenylmethyl ester) group. Completed peptide-resins are suspended in dilute DMF solutions of an appropriate lower alkylamine (such as ethylamine, propylamine, phenethylamine, 1,2-diaminoethane, etc.) and stirred at about 60 °C (for about 18 hrs) whereupon filtration, removal of solvents under reduced pressure and trituration of cleaved peptide oil with ether gives a solid, protected alkylamide peptide. This is then subjected to HF cleavage to remove additional side chain protecting groups and HPLC purification as described in Example 1.

Examples 3-5

Examples 3-5 can be synthesized substantially according to the procedure described in Example 1 using the appropriate protected amino acids to yield the noted peptides.

Example 3: [Aib^8, D-Ala^{17}, $Ala^{18,22,23,27}$, 3-$Pal^{19,31}$, Tle^{16}, $Gaba^{34}$]-GLP-1(7-34)NH_2

Example 4: [Aib^8, D-Ala^{17}, $Ala^{22,23,27}$, 3-$Pal^{19,31}$, Tle^{16}]-GLP-1(7-33)NH_2

Example 5: [Aib^8, D-Ala^{17}, $Ala^{22,23,27}$, 3-$Pal^{19,31}$, $Tle^{16,20}$]-GLP-1(7-33)NH_2

Examples 6-51

Examples 6-51 were made substantially according to the procedure described for Example 1 but using the appropriate protected amino acid to yield the noted peptide. MS were obtained by laser desorption MS (NA means not available).

Example 6: [D-$Ala^{8,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-35)-NH_2; MS = 2971.0; Calc. MS = 2974.4.

Example 7: [$Ala^{18,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-35)-NH_2; MS = 2954.4; Calc. MS = 2958.4.

Example 8: [$Ala^{16,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-35)-NH_2; MS = 2943.0; Calc. MS = 2946.3.

Example 9: [$Ala^{14,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-35)-NH_2; MS = 2956.0; Calc. MS = 2958.4.

Example 10: [$Ala^{22,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-35)-NH_2; MS = 2981.0; Calc. MS = 2988.4.

Example 11: [$Hppa^7$]hGLP-1(7-36)-NH_2; MS = NA

Example 12: [$Ala^{15,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-35)-NH_2; MS = 2928.0; Calc. MS = 2930.4.

Example 13: [$Ala^{17,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-35)-NH_2; MS = 2955.0; Calc. MS = 2958.4.

Example 14: [$Ala^{22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2896.0; Calc. MS = 2888.3.

Example 15: [$Ala^{15,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2852.0; Calc. MS = 2844.3.

Example 16: [$Ala^{17,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2880.0; Calc. MS = 2872.3.

Example 17: [$Ala^{18,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2870.0; Calc. MS = 2872.3.

Example 18: [$Ala^{21,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = NA.

Example 19: [$Ala^{22,23,26,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2832.0; Calc. MS = 2831.2.

Example 20: [$Ala^{22,23,27,32}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2855.0; Calc. MS = 2846.2.

Example 21: [$Ala^{22,23,26,27}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2729.0; Calc. MS = 2732.0.

Example 22: [$Ala^{22,23,27,31}$, 3-Pal^{19}, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2711.6; Calc. MS = 2712.0.

Example 23: [$Ala^{22,23,27,28}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2712.0; Calc. MS = 2713.0.

Example 24: [$Ala^{22,23,27,29}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2746.9; Calc. MS = 2747.1.

Example 25: [$Ala^{23,27}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2777.0; Calc. MS = 2,775.1.

Example 26: [$Ala^{20,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2742.0; Calc. MS = 2747.1.

Example 27: [$Ala^{22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2786.7; Calc. MS = 2789.1.

Example 28: [$Ala^{17,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2771.0; Calc. MS = 2773.1.

Example 29: [D-Ala^{10}, $Ala^{22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{33}$]hGLP-1(7-33)-NH_2; MS = 2802.0; Calc. MS = 2803.2.

Example 30: [D-Ala^{8}, $Ala^{17,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-34)-NH_2; MS = 2905.0; Calc. MS = 2901.3.

Example 31: [$Ala^{17,23,27}$, 3-$Pal^{19,26,31}$]hGLP-1(7-34)-NH_2; MS = 2920.0; Calc. MS = 2921.3.

Example 32: [D-Ala^{8}, Ala^{17}, 3-$Pal^{19,31}$]hGLP-1(7-34)-NH_2; MS = 2908.0 (Na^+ salt); Calc. MS = 2885.3.

Example 33: [$Ala^{17,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-34)-NH_2; MS = 2907.0; Calc. MS = 2901.3.

Example 34: [D-Ala^{8}, $Ala^{17,23,27}$, 3-$Pal^{19,31}$, Tle^{29}]hGLP-1(7-34)-NH_2; MS = 2906.0; Calc. MS = 2901.3.

Example 35: [D-Ala^{8}, $Ala^{17,23,27}$, 3-$Pal^{19,31}$, Tle^{16}]hGLP-1(7-34)-NH_2; MS = 2914.0; Calc. MS = 2915.4.

Example 36: [D-Ala^{8}, $Ala^{17,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2856.8; Calc. MS = 2858.2.

Example 37: [D-Ala^{22}, $Ala^{17,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2871.0; Calc. MS = 2872.3.

Example 38: [Aib^{8}, $Ala^{17,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2875.0; Calc. MS = 2872.3.

Example 39: [D-Ala^{8}, $Ala^{17,22,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-33)-NH_2; MS = 2786.0; Calc. MS = 2787.2.

Example 40: [Aib^{8}, $Ala^{17,22,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-33)-NH_2; MS = 2800.0; Calc. MS = 2801.2.

Example 41: [$Ala^{17,18,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2842.5; Calc. MS = 2842.2.

Example 42: [$Ala^{17,23,27}$, 3-$Pal^{19,31}$, Tle^{33}, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2871.0; Calc. MS = 2872.3.

Example 43: [Tle^{16}, $Ala^{17,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2870.0; Calc. MS = 2872.3.

Example 44: [N-Me-D-Ala^{8}, $Ala^{17,22,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-33)-NH_2; MS = 2795.0; Calc. MS = 2801.2.

Example 45: [Aib^{8}, $Ala^{17,18,22,23,27}$, 3-$Pal^{19,31}$]hGLP-1(7-33)-NH_2; MS = 2784.2; Calc. MS = 2785.2.

Example 46: [$Ala^{17,18,22,23,27}$, 3-$Pal^{19,31}$, $Tle^{16,20}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2871.9; Calc. MS = 2870.3.

Example 47: [D-Ala^{8}, $Ala^{17,18,22,23,27}$, 3-$Pal^{19,31}$, Tle^{16}, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2870.0; Calc. MS = 2870.3.

Example 48: [D-$Ala^{8,22}$, $Ala^{17,18,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2856.3; Calc. MS = 2856.3.

Example 49: [D-$Ala^{8,18}$, $Ala^{17,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = NA.

Example 50: [D-$Ala^{8,17}$, $Ala^{18,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = NA.

Example 51: [D-Ala^{8}, $Ala^{17,18,22,23,27}$, 3-$Pal^{19,31}$, $Gaba^{34}$]hGLP-1(7-34)-NH_2; MS = 2861.6; Calc. MS = 2856.3.

Example 52

[Aib^{8}, $A6c^{32}$]hGLP-1(7-36)NH_2

The title peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnoize, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-Methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.93 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-Thr(Bzl)-OH, Boc-A6c-OH, Ser(Bzl)-OH, Boc-Phe-OH, Boc-Aib-OH, Boc-Glu(OcHex)-OH and Boc-Trp(Fm)-OH. The synthesis was carried out on a 0.20 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 ml) in 4 ml of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were about 5 min except for the Boc-Aib-OH and Boc-A6c-OH residues and the following residues, Boc-Trp(Fm)-OH and

Boc-His(DNP)-OH wherein the coupling times were about 2 hours.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min), the formyl group on the side of the chain of Trp was removed by treatment with a solution of 15% ethanolamine/ 15% water/ 70% DMF for 2 x 30 min. The partially-deprotected peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 ml of HF containing 1 ml of anisole and dithiothreitol (24 mg) at 0 °C for about 75 min. HF was removed with a flow of nitrogen. The residue was washed with ether (6 x 10 ml) and extracted with 4N HOAc (6 x 10 ml).

The peptide mixture in the aqueous extract was purified on a reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC® C_{18} column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (20% to 50% of solution B over 105 min) at a flow rate of 10 ml/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 92 mg of a white solid was obtained. Purity was >99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3324.2 (the calculated molecular weight is 3323.7).

The synthesis of other compounds of the present invention can be carried out in the same manner as described for the synthesis of [Aib^8, A6c^{32}]hGLP-1(7-36)NH_2 in Example 52 above but using the appropriate protected amino acids depending on the desired peptide.

[(N$^\alpha$-HEPES-His)^7]hGLP-1(7-36)NH_2 {HEPES is (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid)} can be synthesized as follows: After assembly of the peptide long chain on MBHA resin (0.20 mmol), the peptide-resin is treated with 100% TFA (2 x 2 min.) and washed with DMF and DCM. The resin is then neutralized with 10% DIEA in DMF for about 2 min. After washing with DMF and DCM, the resin is treated with 0.23 mmol of 2-chloro-1-ethanesulfonyl chloride and 0.7 mmol of DIEA in DMF for about 1 hour. The resin is washed with DMF and DCM and treated with 1.2 mmol of 2-hydroxyethylpiperazine for about 2 hours. The resin is washed with DMF and DCM and treated with different reagents ((1) 20% mercaptoethanol / 10% DIEA in DMF and (2) 15% ethanolamine / 15% water / 70% DMF) to remove the DNP group from the His side chain and formyl group on the Trp

side chain as described above before the final HF cleavage of the peptide from the resin.

[(N^{α}-HEPA-His)^{7}]hGLP-1(7-36)NH_2 ([(4-(2-hydroxyethyl)-1-piperazineacetyl)-His^{7}]hGLP-1(7-36)NH_2) can be made substantially according to the procedure described immediately above for making [(N^{α}-HEPES-His)^{7}]hGLP-1(7-36)NH_2 except that 2-bromo-acetic anhydride is used in place of 2-chloro-1-ethanesulfonyl chloride.

Examples 53-90

Examples 53-90 were made substantially according to Example 52 but using the appropriate protected amino acid.

Example 53: [A6c^{20,32}]hGLP-1(7-36)-NH_2; MS =3322.3 ; Calc. MW = 3321.7.

Example 54: [Aib^{8}]hGLP-1(7-36)-NH_2; MS = 3311.7; Calc. MW = 3311.7.

Example 55: [(Tma-His)^{7}]hGLP-1(7-36)-NH_2 ; MS = 3395.9; Calc. MW = 3396.9.

Example 56: [A6c^{8}]hGLP-1(8-36)-NH_2; MS = 3214.5; Calc. MW = 3214.7.

Example 57: [A6c^{8}]hGLP-1(7-36)-NH_2; MS = 3351.5; Calc. MW = 3351.8.

Example 58: [A6c^{16,20}]hGLP-1(7-36)-NH_2; MS = 3335.9; Calc. MW = 3335.8.

Example 59: [A6c^{29,32}]hGLP-1(7-36)-NH_2; MS = 3321.7; Calc. MW = 3321.7.

Example 60: [A6c^{20}, Aib^{24}]hGLP-1(7-36)-NH_2; MS = 3323.6; Calc. MW = 3323.7.

Example 61: [Aib^{24}, A6c^{29,32}]hGLP-1(7-36)-NH_2; MS = 3335.7; Calc. MW = 3335.8.

Example 62: [A6c^{16,29,32}]hGLP-1(7-36)-NH_2; MS = 3347.7; Calc. MW = 3347.8.

Example 63: [Ura^{7}]hGLP-1(7-36)-NH_2; MS = 3279.5; Calc. MW = 3280.7.

Example 64: [Paa^{7}]hGLP-1(7-36)-NH_2; MS = 3290.9; Calc. MW = 3291.8.

Example 65: [Pta^{7}]hGLP-1(7-36)-NH_2; MS = 3311.2; Calc. MW = 3311.8.

Example 66: [N-Me-Ala^{8}]hGLP-1(7-36)-NH_2; MS = 3311.4; Calc. MW = 3311.7.

Example 67: [N-Me-D-Ala^{8}]hGLP-1(7-36)-NH_2; MS = 3311.6; Calc. MW = 3311.7.

Example 68: [N-Me-D-Ala^{8}]hGLP-1(8-36)-NH_2; MS = 3174.0; Calc. MW = 3174.6.

Example 69: [N-Me-Gly^{8}]hGLP-1(7-36)-NH_2; MS = 3297.3; Calc. MW = 3297.7.

Example 70: [A5c^{8}]hGLP-1(7-36) ; MS = 3337.3; Calc. MW = 3337.8.

Example 71: [N-Me-Glu^{9}]hGLP-1(7-36)-NH_2; MS = 3311.4; Calc. MW = 3311.7.

Example 72: [A5c^{8}, A6c^{20,32}]hGLP-1(7-36)-NH_2; MS = 3361.4; Calc. MW = 3361.8.

Example 73: [Aib^{8}, A6c^{32}]hGLP-1(7-36)-NH_2; MS = 3323.2; Calc. MW = 3323.7.

Example 74: [Aib^{8,25}]hGLP-1(7-36)-NH_2; MS = 3325.8; Calc. MW = 3325.7.

Example 75: [Aib^{8,24}]hGLP-1(7-36)-NH_2; MS = 3325.8; Calc. MW = 3325.7.

Example 76: [Aib^{8,30}]hGLP-1(7-36)-NH_2; MS = 3326.1; Calc. MW = 3325.7.

Example 77: [Aib^{8}, Cha^{20}]hGLP-1(7-36)-NH_2; MS = 3351.8; Calc. MW = 3351.8.

Example 78: [Aib^{8}, Cha^{32}]hGLP-1(7-36)-NH_2; MS = 3352.0; Calc. MW = 3351.8.

Example 79: [Aib^8, Glu^{23}]hGLP-1(7-36)-NH_2; MS = 3311.7; Calc. MW = 3312.7.
Example 80: [Aib^8, $A6c^{20}$]hGLP-1(7-36)-NH_2; MS = 3323.6; Calc. MW = 3323.7.
Example 81: [Aib^8, $A6c^{20,32}$]hGLP-1(7-36)-NH_2; MS = 3335.3; Calc. MW = 3335.7.
Example 82: [$Aib^{8,22}$]hGLP-1(7-36)-NH_2; MS = 3339.8; Calc. MW = 3339.8.
Example 83: [Aib^8,β-Ala^{22}]hGLP-1(7-36)-NH_2; MS = 3325.6; Calc. MW = 3325.8.
Example 84: [Aib^8, Lys^{25}]hGLP-1(7-36)-NH_2; MS = 3369.0; Calc. MW = 3368.8.
Example 85: [Aib^8, $A6c^{12}$]hGLP-1(7-36)-NH_2; MS = 3289.8; Calc. MW = 3289.7.
Example 86: [Aib^8, $A6c^{29}$]hGLP-1(7-36)-NH_2; MS = 3323.9; Calc. MW = 3323.7.
Example 87: [Aib^8, $A6c^{33}$]hGLP-1(7-36)-NH_2; MS = 3338.0; Calc. MW = 3337.8.
Example 88: [$Aib^{8,14}$]hGLP-1(7-36)NH_2; MS = 3309.8; Calc. MW = 3309.7.
Example 89: [$Aib^{8,18}$]hGLP-1(7-36)NH_2; MS = 3309.7; Calc. MW = 3309.7.
Example 90: [$Aib^{8,17}$]hGLP-1(7-36)NH_2; MS = 3309.4; Calc. MW = 3309.7.

Example 91

[Aib^8, $A5c^{33}$]hGLP-1 (7-36)NH_2

The title compound can be made substantially according to Example 52 using the appropriate protected amino acids.

Example 92

[Aib^8, $A6c^{32}$, Lys^{36}(N^ε-tetradecanoyl)]hGLP-1(7-36)NH_2

The Boc amino acids to be used are the same as those in the synthesis of [Aib^8, $A6c^{32}$]hGLP-1(7-36)NH_2 (Example 52) except that Fmoc-Lys(Boc)-OH is used here for the Lys^{36}(N^ε-tetradecanoyl) residue. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 ml of 0.5N HBTU in DMF. To the solution is added 1 ml of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA resin (substitution = 0.93 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF. Myristic acid (2.5 mmol) is pre-activated with HBTU (2.0 mmol) and DIEA (1.0 ml) in 4 ml of DMF for 2 min and is coupled to the Fmoc-Lys-resin. The coupling time is about 1 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The remainder of the synthesis and purification procedures of the peptide are the same as those in the synthesis of [Aib^8, $A6c^{32}$]hGLP-1(7-36)NH_2.

The syntheses of other compounds containing Lys(N^ε-alkanoyl) residue are carried out in an analogous manner as described for the synthesis of [Aib^8, $A6c^{32}$, Lys^{36}(N^ε-

octanoyl)]hGLP-1(7-36)NH_2. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^{ϵ}-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N^{ϵ}-alkanoyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^{ϵ}-alkanoyl) residue is assembled on the resin on the peptide synthesizer first.

Examples 93-98

Examples 93-98 can be made substantially according to the procedure described for Example 92 using the appropriate amino acids.

Example 93: [Aib^{8}, $A6c^{32}$, Lys^{36}(N^{ϵ}-tetradecanoyl)]hGLP-1(7-36)NH_2

Example 94: [Aib^{8}, $Arg^{26,34}$, $A6c^{32}$, Lys^{36}(N^{ϵ}-tetradecanoyl)]hGLP-1(7-36)NH_2

Example 95: [Aib^{8}, Arg^{26}, $A6c^{32}$, Lys^{34}(N^{ϵ}-tetradecanoyl)]hGLP-1(7-36)NH_2

Example 96: [Aib^{8}, Lys^{26}(N^{ϵ}-tetradecanoyl), $A6c^{32}$, Arg^{34}]hGLP-1(7-36)NH_2

Example 97: [Aib^{8}, Lys^{36}(N^{ϵ}-octanoyl)]hGLP-1 (7-36)NH_2

Example 98: [Aib^{8}, $A6c^{20,32}$, Lys^{36}(N^{ϵ}-octanoyl)]hGLP-1 (7-36)NH_2

Example 99

[Aib^{8}, $Arg^{26,34}$, $A6c^{32}$, Lys^{36}(N^{ϵ}-tetradecanoyl)]hGLP-1(7-36)-OH

The Boc amino acids to be used are the same as those used in the synthesis of [Aib^{8}, $A6c^{32}$, Lys^{36}(N^{ϵ}-tetradecanoyl)]hGLP-1(7-36)NH_2 (Example 92). Fmoc –Lys(Boc)-OH (2.5 mmol) is pre-activated with HBTU (2.0 mmol), HOBt (2.0 mmol) and DIEA (2.5 ml) in DMF (4 ml) for about 2 min. This amino acid is coupled to 235 mg of PAM resin (Chem-Impex, Wood Dale, IL; substitution = 0.85 mmol/g) manually on a shaker. The coupling time is about 8 hrs. The remainder of the synthesis and purification procedures for making the peptide are the same as those described in Example 52.

The syntheses of other analogs of hGLP-1(7-36)-OH and hGLP-1(7-37)-OH, which contain Lys(N^{ϵ}-alkanoyl) residue, are carried out in an analogous manner as described for the synthesis of [Aib^{8}, $Arg^{26,34}$, $A6c^{32}$, Lys^{36}(N^{ϵ}-tetradecanoyl)]hGLP-1(7-36)-OH. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^{ϵ}-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys.

Examples 100-103

Examples 100-103 can be made substantially according to the procedure described for Example 99 using the appropriate amino acids.

Example 100: [Aib^{8}, Arg^{26}, $A6c^{32}$, Lys^{34}(N^{ϵ}-tetradecanoyl)]hGLP-1(7-36)-OH

Example 101: [Aib^{8}, Lys^{26}(N^{ϵ}-tetradecanoyl), $A6c^{32}$, Arg^{34}]hGLP-1(7-36)-OH

Example 102: [Aib^{8}, Arg^{26,34}, A6c^{32}, Lys^{36}(N^{ε}-tetradecanoyl)]hGLP-1(7-37)-OH

Example 103: [Aib^{8}, Arg^{26}, A6c^{32},Lys^{34}(N^{ε}-tetradecanoyl)]hGLP-1(7-37)-OH

CLAIMS

What is claimed is:

1. A compound of formula (I),

(R^2R^3)- A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}–A^{37}- R^1,

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, D-His, Tyr, 3-Pal, 4-Pal, Hppa, Tma-His, Amp or deleted, provided that when A^7 is Ura, Paa, Pta or Hppa then R^2 and R^3 are deleted;

A^8 is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala, Arg or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, Ala, D-Ala, Phe or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β-Nal, Cha, Trp or X^1-Phe;

A^{13} is Thr or Ser;

A^{14} is Ser, Thr, Ala or Aib;

A^{15} is Asp, Ala, D-Asp or Glu;

A^{16} is Val, D-Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala, D-Ala, Tba or Cha;

A^{17} is Ser, Ala, D-Ala, Aib, Acc or Thr;

A^{18} is Ser, Ala, D-Ala, Aib, Acc or Thr;

A^{19} is Tyr, D-Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β-Nal, Amp or X^1-Phe;

A^{20} is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X^1-Phe;

A^{21} is Glu, Ala or Asp;

A^{22} is Gly, Acc, Ala, D-Ala, β-Ala or Aib;

A^{23} is Gln, Asp, Ala, D-Ala, Aib, Acc, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{26} is Lys, Ala, 3-Pal, 4-Pal, Arg, hArg, Orn, Amp, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{27} is Glu, Ala, D-Ala or Asp;

A^{28} is Phe, Ala, Pal, β-Nal, X^1-Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala, Tba or Phe;

A^{30} is Ala, Aib, Acc or deleted;

A^{31} is Trp, Ala, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib, Cha, Amp or deleted;

A^{32} is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X^1-Phe, Ala or deleted;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, X^1-Phe, Tba, Gaba or deleted;

A^{34} is Lys, Arg, hArg, Orn, Amp, Gaba, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) or deleted;

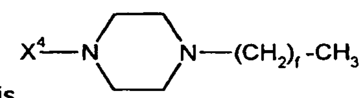
A^{35} is Gly or deleted;

A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, Amp, HN-CH($(CH_2)_n$-$NR^{10}R^{11}$)-C(O), HN-CH($(CH_2)_e$-X^3)-C(O) or deleted;

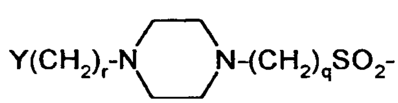
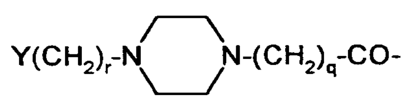
A^{37} is Gly or deleted;

X^1 for each occurrence is independently selected from the group consisting of (C_1-C_6)alkyl, OH and halo;

R^1 is OH, NH_2, (C_1-C_{12})alkoxy, or NH-X^2-CH_2-Z, wherein X^2 is a (C_1-C_{12})hydrocarbon moiety, and Z is H, OH, CO_2H or $CONH_2$;

X^3 is  or –C(O)-NHR^{12}, wherein X^4 for each occurrence is independently -C(O)-, -NH-C(O)- or -CH_2-, and f for each occurrence is independently an integer from 1 to 29;

each of R^2 and R^3 is independently selected from the group consisting of H, (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, and hydroxynaphthyl(C_1-C_{30})alkyl; or one of R^2 and R^3 is C(O)X^5 in which X^5 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, hydroxynaphthyl(C_1-C_{30})alkyl, $(CH_3)_2$-N-C=$\overset{+}{N}(CH_3)_2$,

 or ,

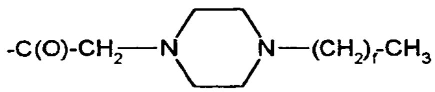
(a) (b)

where Y is H or OH, r is 0 to 4 and q is 0 to 4;

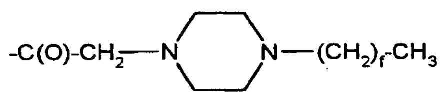
e for each occurrence is independently an integer from 1 to 4;

n for each occurrence is independently an integer from 1-5; and

R^{10} and R^{11} for each occurrence is each independently H, $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or



, provided that when R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or



, R^{11} is H or $(C_1\text{-}C_{30})$alkyl; and

R^{12} is $(C_1\text{-}C_{30})$alkyl;

with the proviso that:

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, or -37)NH_2 or hGLP-1(7-36, or -37)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, or -37)NH_2 or hGLP-1(7-36, or -37)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not [Lys^{26}(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, [Lys^{34}(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, [$Lys^{26,34}$-bis(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, [Arg^{26}, Lys^{34}(N^{ε}-alkanoyl)]hGLP-1(8-36, or -37)-E, or [$Arg^{26,34}$, Lys^{36}(N^{ε}-alkanoyl)]hGLP-1(7-36, or -37)-E, wherein E is -OH or -NH_2;

(iv) a compound of formula (I) is not Z-hGLP-1(7-36, or -37)-OH, Z-hGLP-1(7-36, or -37)-NH_2, where Z is selected from the group consisting of

(e) [Arg^{26}], [Arg^{34}], [$Arg^{26,34}$], [Lys^{36}], [Arg^{26}, Lys^{36}], [Arg^{34}, Lys^{36}], [D-Lys^{36}], [Arg^{36}], [D-Arg^{36}], [$Arg^{26,34}$, Lys^{36}] or [$Arg^{26,36}$, Lys^{34}];

(f) [Asp^{21}];

(g) at least one of [Aib^{8}], [D-Ala^{8}] and [Asp^{9}]; and

(h) [Tyr^{7}], [N-acyl-His^{7}], [N-alkyl-His^{7}], [N-acyl-D-His^{7}] or [N-alkyl-D-His^{7}];

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not [N-Me-Ala^{8}]hGLP-1(8-36 or -37), [Glu^{15}]hGLP-1(7-36 or -37), [Asp^{21}]hGLP-1(7-36 or -37) or [Phe^{31}]hGLP-1(7-36 or -37).

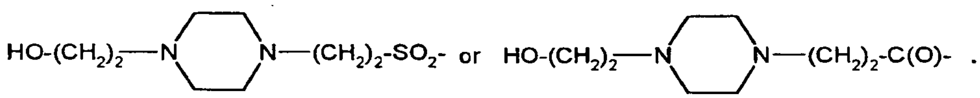
2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof wherein A^{11} is Thr; A^{13} is Thr; A^{14} is Ser, Aib or Ala; A^{17} is Ser, Ala, Aib or D-Ala; A^{18} is Ser, Ala, Aib or D-Ala; A^{21} is Glu or Ala; A^{23} is Gln, Glu, or Ala; and A^{27} is Glu or Ala.

3. A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc or Aic; A^{16} is Val, D-Val, Acc, Aib, Ala, Tle or D-Ala; A^{19} is Tyr, 3-Pal, 4-Pal or D-Tyr; A^{20} is Leu, Acc, Cha, Ala or Tle; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-NH-R^{10})-C(O); A^{28} is Phe or Ala; A^{29} is Ile, Acc or Tle; A^{30} is Ala, Aib or deleted; A^{31} is Trp, Ala, 3-Pal, 4-Pal or deleted; A^{32} is Leu, Acc, Cha, Ala or deleted; A^{33} is Val, Acc, Ala, Gaba, Tle or deleted.

4. A compound according to claim 3 or a pharmaceutically acceptable salt thereof wherein A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly, Ala, D-Ala or Phe; A^{12} is Phe, A6c or A5c; A^{16} is Val, Ala, Tle, A6c, A5c or D-Val; A^{20} is Leu, A6c, A5c, Cha, Ala or Tle; A^{22} is Gly, Aib, β-Ala, L-Ala or D-Ala; A^{24} is Ala or Aib; A^{29} is Ile, A6c, A5c or Tle; A^{32} is Leu, A6c, A5c, Cha, Ala or deleted; A^{33} is Val, A6c, A5c, Ala, Gaba, Tle or deleted.

5. A compound according to claim 4 or a pharmaceutically acceptable salt thereof wherein R^1 is OH or NH_2.

6. A compound according to claim 5 or a pharmaceutically acceptable salt thereof wherein R^2 is H and R^3 is $(C_1$-$C_{30})$alkyl, $(C_2$-$C_{30})$alkenyl, $(C_1$-$C_{30})$acyl,



7. A compound according to claim 1 wherein said compound is

[D-Ala^8, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]-GLP-1(7-34)NH_2;
[D-Ala^{8,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH_2;
[Ala^{18,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH_2;
[Ala^{16,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH_2;
[Ala^{14,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH_2;
[Ala^{22,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH_2;
[Hppa^7]hGLP-1(7-36)-NH_2;
[Ala^{15,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH_2;
[Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH_2;
[Ala^{22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Ala^{15,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;

[Ala^{21,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Ala^{22,23,27,32}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[Ala^{22,23,27,31}, 3-Pal^{19}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[Ala^{22,23,27,28}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[Ala^{22,23,27,29}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[Ala^{23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[Ala^{20,22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[Ala^{22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[D-Ala^{10}, Ala^{22,23,27}, 3-Pal^{19,31}, Gaba^{33}]hGLP-1(7-33)-NH_2;
[D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH_2;
[Ala^{17,23,27}, 3-Pal^{19,26,31}]hGLP-1(7-34)-NH_2;
[D-Ala^{8}, Ala^{17}, 3-Pal^{19,31}]hGLP-1(7-34)-NH_2;
[Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH_2;
[D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Tle^{29}]hGLP-1(7-34)-NH_2;
[D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Tle^{16}]hGLP-1(7-34)-NH_2;
[D-Ala^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[D-Ala^{22}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Aib^{8}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[D-Ala^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH_2;
[Aib^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH_2;
[Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Ala^{17,23,27}, 3-Pal^{19,31}, Tle^{33}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[Tle^{16}, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[N-Me-D-Ala^{8}, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH_2;
[Aib^{8}, Ala^{17,18,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH_2;
[Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle^{16,20}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[D-Ala^{8}, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle^{16}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[D-Ala^{8,22}, Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[D-Ala^{8,18}, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2;
[D-Ala^{8,17}, Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2; or

[D-Ala^{8}, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Gaba^{34}]hGLP-1(7-34)-NH_2; or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1 wherein said compound is
[Aib^{8}, A6c^{32}]hGLP-1(7-36)NH_2;
[A6c^{20,32}]hGLP-1(7-36)-NH_2;
[Aib^{8}]hGLP-1(7-36)-NH_2;
[(Tma-His)^{7}]hGLP-1(7-36)-NH_2 ;
[A6c^{8}]hGLP-1(8-36)-NH_2;
[A6c^{8}]hGLP-1(7-36)-NH_2;
[A6c^{16,20}]hGLP-1(7-36)-NH_2;
[A6c^{29,32}]hGLP-1(7-36)-NH_2;
[A6c^{20}, Aib^{24}]hGLP-1(7-36)-NH_2;
[Aib^{24}, A6c^{29,32}]hGLP-1(7-36)-NH_2;
[A6c^{16,29,32}]hGLP-1(7-36)-NH_2;
[Ura^{7}]hGLP-1(7-36)-NH_2;
[Paa^{7}]hGLP-1(7-36)-NH_2;
[Pta^{7}]hGLP-1(7-36)-NH_2;
[N-Me-Ala^{8}]hGLP-1(7-36)-NH_2;
[N-Me-D-Ala^{8}]hGLP-1(7-36)-NH_2;
[N-Me-D-Ala^{8}]hGLP-1(8-36)-NH_2;
[N-Me-Gly^{8}]hGLP-1(7-36)-NH_2;
[A5c^{8}]hGLP-1(7-36) ;
[N-Me-Glu^{9}]hGLP-1(7-36)-NH_2;
[A5c^{8}, A6c^{20,32}]hGLP-1(7-36)-NH_2;
[Aib^{8}, A6c^{32}]hGLP-1(7-36)-NH_2;
[Aib^{8,25}]hGLP-1(7-36)-NH_2;
[Aib^{8,24}]hGLP-1(7-36)-NH_2;
[Aib^{8,30}]hGLP-1(7-36)-NH_2;
[Aib^{8}, Cha^{20}]hGLP-1(7-36)-NH_2;
[Aib^{8}, Cha^{32}]hGLP-1(7-36)-NH_2;
[Aib^{8}, Glu^{23}]hGLP-1(7-36)-NH_2;
[Aib^{8}, A6c^{20}]hGLP-1(7-36)-NH_2;
[Aib^{8}, A6c^{20,32}]hGLP-1(7-36)-NH_2;
[Aib^{8,22}]hGLP-1(7-36)-NH_2;

[Aib^8,β-Ala^{22}]hGLP-1(7-36)-NH_2;
[Aib^8, Lys^{25}]hGLP-1(7-36)-NH_2;
[Aib^8, $A6c^{12}$]hGLP-1(7-36)-NH_2;
[Aib^8, $A6c^{29}$]hGLP-1(7-36)-NH_2;
[Aib^8, $A6c^{33}$]hGLP-1(7-36)-NH_2;
[$Aib^{8,14}$]hGLP-1(7-36)NH_2;
[$Aib^{8,18}$]hGLP-1(7-36)NH_2; or
[$Aib^{8,17}$]hGLP-1(7-36)NH_2; or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

10. A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

11. A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

12. A method according to claim 11 wherein said disease is Type I diabetes or Type II diabetes.

ABSTRACT

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

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Docket No.
BPC077

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

GLP-1 ANALOGUES

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on ______________ as United States Application No. or PCT International Application Number ______________
and was amended on ______________
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

John D. Conway, Reg. No. 39,150
Brian R. Morrill, Reg. No. 42,908
Y. Rocky Tsao, Reg. No. 34,053
Eric L. Prahl, Reg. No. 32,590
Frank R. Occhiutti, Reg. No. 35,306

Send Correspondence to: **John D. Conway**
BIOMEASURE, INC.
27 Maple Street
Milford, MA 01757-3650

Direct Telephone Calls to: *(name and telephone number)*
John D. Conway, (508) 478-0144

Full name of sole or first inventor **Zheng Xin Dong**	
Sole or first inventor's signature	Date
Residence **Framingham, Massachusetts**	
Citizenship **China**	
Post Office Address **40 Angelica Drive, Framingham, MA 01701**	

Full name of second inventor, if any **David H. Coy**	
Second inventor's signature	Date
Residence **New Orleans, Louisiana**	
Citizenship **United States**	
Post Office Address **1529 Fourth Street, New Orelcans, LA 70130**	